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Title: Lumped-Parameter and Finite Element Modeling of Heart Failure with Preserved Ejection Fraction

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Author Questionnaire

1. Microscopy: Does your protocol demonstrate the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or similar? **N**

2. Software: Does the part of your protocol being filmed demonstrate software usage? **Y**

3. Interview statements: Considering the Covid-19-imposed mask-wearing and social distancing recommendations, which interview statement filming option is the most appropriate for your group? **Please select one**.

☒ Interviewees wear masks until the videographer steps away (≥6 ft/2 m) and begins filming. The interviewee then removes the mask for line delivery only. When the shot is acquired, the interviewee puts the mask back on. Statements can be filmed outside if weather permits.

Note: Videographers would need to fill out daily health attestations whether indoors or out. We are still in the process of checking whether there is any current policy linked to this type of activity at Massachusetts Institute of Technology.

3. Filming location: Will the filming need to take place in multiple locations (greater than walking distance)? **N**

Protocol Length
Number of Shots: **30**

Introduction

1. Introductory Interview Statements

REQUIRED:

1.1. **Luca Rosalia**: This protocol can be used to recapitulate acute pressure overload, as well as chronic loss of ventricular compliance, to investigate the effects of Heart Failure with Preserved Ejection Fraction on cardiovascular hemodynamics **[1]**.

1.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

REQUIRED:

1.2. **Caglar Ozturk**: Our lumped-parameter model is very computationally efficient. The finite element approach integrates the electrical and structural domains for a more accurate modeling of cardiovascular hemodynamics **[1]**.

1.2.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

OPTIONAL:

1.3. **Luca Rosalia**: There is a strong clinical need for effective treatments for HFpEF. Computational methods like ours are paramount in the development and regulatory approval of medical devices and therapeutics **[1]**.

1.3.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

Protocol

2. Zero-Dimensional (0D) Lumped-Parameter Model

2.1. To set up a zero-dimension lumped-parameter model, after constructing a domain in the numerical solver environment as illustrated **[1]**, navigate to the hydraulics library to find the required elements **[2]** and drop the hydraulic pipeline elements into the workspace **[3-TXT]**.

2.1.1. LAB MEDIA: Figure 1
2.1.2. WIDE: Talent at computer, navigating library
2.1.3. SCREEN: screenshot_1: 00:30-00:45 *Video Editor: please speed up* **TEXT: Valve elements can also be added at this time**

2.2. Insert the constant volume hydraulic chamber elements to define the wall compliance and fluid compressibility **[1]** and add the linear resistance elements to define the resistance to flow **[2]**.

2.2.1. SCREEN: screenshot_2: 00:00-00:26 *Video Editor: please speed up*
2.2.2. SCREEN: screenshot_2: 00:28-00:47 *Video Editor: please speed up*

2.3. Model the contractility of each heart chamber through the custom variable-compliance compliance chamber element **[1]** and provide the parameters relative to each element as illustrated in the Table **[2]**.

2.3.1. SCREEN: screenshot_3: 00:03-01:02 *Video Editor: please speed up*
2.3.2. LAB MEDIA: Table S1 *Video Editor: please sequentially emphasize each data column or no animation*

2.4. Then insert a Physical Signal Repeating Sequence element for each of the blocks that require a time-varying user-defined input signal, select the default **ODE 23t** (O-D-E twenty-three-T) **implicit solver**, and run the simulation for 100 seconds to reach a steady state **[1]**.

2.4.1. SCREEN: screenshot_4: 00:04-01:37 *Video Editor: please speed up*

3. Finite Element Analysis (FEA) Model

3.1. To set up a finite element analysis model, navigate to the **Electrical** domain **[1]** and select the **Standard** module **[2]**.

3.1.1. WIDE: Talent opening Elec domain, with monitor visible in frame
3.1.2. SCREEN: screenshot_5 *Video Editor: please speed up*

3.2. Select the single-analysis **BEAT** step, set the duration of the cardiac cycle to 500 milliseconds, and apply an electrical potential pulse to a node set representing the sinoatrial node **[1]**.

3.2.1. SCREEN: screenshot_6

3.3. After reviewing the default electrical waveform **[1]**, launch the **Job** module and create a **heart-electrical** job **[1]**.

3.3.1. SCREEN: screenshot_7: 00:00-00:25 *Video Editor: please speed up*
3.3.2. SCREEN: screensht_7: 00:26-00:47 *Video Editor: please speed up*

3.4. Once the electrical analysis setup is complete, navigate to the **Mechanical** domain. In the **PRE-LOAD** step, review the boundary conditions of the pre-stressed state of the heart and select 0.3 seconds as the step time **[1]**.

3.4.1. SCREEN: screenshot_8: 00:00-00:18 *Video Editor: please speed up*

3.5. In the **BEAT1** step, use 0.5 seconds as the step time to simulate contraction. In the **RECOVERY1** step, select 0.5 seconds for cardiac relaxation and ventricular filling for a heart rate of 60 beats per minute **[1]**.

3.5.1. SCREEN: screenshot_9: 00:00-00:16 *Video Editor: please speed up*

3.6. Launch the **Job** module and create a **heart-mechanical** job. Enable the **double precision** option **[1]**.

3.6.1. SCREEN: screenshot_10: 00:00-00:21

3.7. Review the simplified lumped-parameter Windkessel model and the blood flow model representation, adjusting the values of the resistive and capacitive elements for the flow resistances and structural compliances, respectively, as necessary **[1]**.

3.7.1. SCREEN: screenshot_11 *Video Editor: please speed up*

3.8. Review the 3D finite element representation of the four heart chambers and confirm that their geometrical positions are accurate **[1]**.

3.8.1. SCREEN: screenshot_12 *Video Editor: please speed up*

3.9. After checking the heart assembly, switch to the **Interaction** module to adjust the compliance and contractility values of each of the four heart chambers **[1]**.

3.9.1. SCREEN: screenshot_13: 00:00-00:30 *Video Editor: please speed up*

3.10. Review the stiffness value to model the pressure-volume response in the arterial, venous, and pulmonary circulations **[1]** and adjust the viscous resistance coefficient to modify the blood flow model in each fluid exchange link **[2]**.

3.10.1. SCREEN: screenshot_14: 00:00-00:15 *Video Editor: please speed up*
3.10.2. SCREEN: screenshot_14: 00:16-00:30 *Video Editor: please speed up*

3.11. For a multiphysics simulation, insert the input, object, and library files into the working directory **[1]** and launch the finite element analysis model simulation software **[1]**.

3.11.1. SCREEN: screenshot_15: 00:00-00:10
3.11.2. SCREEN: screenshot_15: 00:18-00:26

3.12. Run the electrical simulation **heart-electrical** job and confirm that the resulting **.odb** (O-D-B) file is in the working directory **[1]**.

3.12.1. SCREEN: screenshot_16: 00:00-00:20 *Video Editor: please speed up*
3.12.2. SCREEN: screenshot_16: 00:30-00:39

3.13. Switch to the **Mechanical** domain to move to the second simulation phase. In the **PRE-LOAD** step, use the built-in smooth amplitude option to increase the pressure level from zero to the desired level **[2]**.

3.13.1. SCREEN: screenshot_17: 00:14-00:23

3.14. Then disable the pressure boundary conditions to run the blood flow model with a constant overall blood volume within the circulation system **[1]** and run the **heart-mech** simulation job **[2]**.

3.14.1. SCREEN: screenshot_18: 00:00-00:10
3.14.2. SCREEN: screenshot_18: 00:17-00:30 *Video Editor: please speed up*

4. Aortic Valve Stenosis

4.1. To simulate aortic valve stenosis in the lumped-parameter model, in the left ventricular compartment **[1]**, modify the input signal relative to the aortic valve and simulate a reduction of the orifice area equal to 70% compared to baseline **[2]**.

4.1.1. WIDE: Talent opening/navigating to the left ventricular compartment
4.1.2. SCREEN: screenshot_19 *Video Editor: please speed up*

4.2. To simulate aortic valve stenosis in the FEA model, modify the fluid exchange definition of the **LINK-Left Ventricle-ARTERIAL** parameter **[1]** and execute the toolbox files to perform an inverse mechanical simulation **[2]**.

4.2.1. SCREEN: screenshot_20: 00:10-00:23
4.2.2. SCREEN: screenshot_20: 01:03-01:30 *Video Editor: please speed up*

4.3. Once the inverse mechanical simulation is complete, run the post-processing functions as indicated **[1]**. Then launch the **Job** module and create a **heart-mech** job to run a new mechanical simulation as demonstrated **[2]**.

4.3.1. SCREEN: screenshot_21: 00:00-00:39 *Video Editor: please speed up*
4.3.2. SCREEN: screenshot_21: 00:44-00:54

5. Heart Failure with Preserved Ejection Fraction (HFpEF) Hemodynamics

5.1. To mimic wall stiffening due to pressure-overload in the lumped-parameter model **[1]**, modify the left ventricular diastolic compliance of the left ventricle compliance element and increase the leak resistance of the left ventricle pump to 18×10^6 pascals/second/meter **[2]**.

5.1.1. WIDE: Talent navigating to LV compliance element
5.1.2. SCREEN: screenshot_22: 00:00-00:24 *Video Editor: please speed up*

5.2. To simulate the effects of chronic remodeling in the finite element analysis model, edit the active material properties of the left ventricle geometry **[1]** and modify the material response of the left ventricle in the **mechanical-material-Left ventricle_ACTIVE** file **[2]**.

5.2.1. SCREEN: screenshot_23: 00:00-00:32 *Video Editor: please speed up*
5.2.2. SCREEN: screenshot_23: 00:35-00:45

5.3. To capture the increased stiffness response for the heart failure with preserved ejection fraction physiology, increase the *a* and *b* stiffness parameters in the anisotropic hyperelastic formulation **[1]**.

5.3.1. SCREEN: screenshot_24: 00:00-00:12 *Video Editor: please speed up*

5.4. In the **PRE-LOAD** step, set the fluid cavity pressures of the left ventricle and left atrium to 20 millimeters per mercury **[1]** and perform an inverse mechanical stimulation to obtain the volumetric state of the left ventricle and atrium **[2]**.

5.4.1. SCREEN: screenshot_25: 00:02-00:13
5.4.2. SCREEN: screenshot_25: 00:15-00:37 *Video Editor: please speed up*

5.5. Then execute the post-processing functions as indicated and perform a new mechanical simulation as demonstrated **[1]**.

5.5.1. SCREEN: screenshot_26 *Video Editor: please speed up*

Protocol Script Questions

A. Which steps from the protocol are the most important for viewers to see? Please list 4 to 6 individual steps.
n/a

B. What is the single most difficult aspect of this procedure and what do you do to ensure success? Please list 1 or 2 individual steps from the script above.
In the lumped-parameter model, it is critical that the network is accurately recreated (Step 2.1), as shown in Figure 1, and that input parameters of each element are defined correctly (Table S1-S2).

Functioning of the FEA model requires all the simulation files that are packaged with the solver (Step 3.11) that are listed in Table S5. Omission of any of the prerequisite components might cause early termination of the simulation.

Results

6. **Results: Representative Lumped-Parameter and FEA Heart Failure Modeling**

6.1. The two in silico models show similar aortic **[1]** and left ventricular hemodynamics within the physiologic range **[2]**.

6.1.1. LAB MEDIA: Figure 3 *Video Editor: please emphasize dashed data lines*
6.1.2. LAB MEDIA: Figure 3 *Video Editor: please emphasize solid data lines*

6.2. Under aortic stenosis conditions **[1]**, pressure and volume waveforms demonstrate a 70% reduction of the aortic valve orifice area in both models **[2]**.

6.2.1. LAB MEDIA: Figure 4
6.2.2. LAB MEDIA: Figure 4 *Video Editor: please emphasize dashes data line in both graphs*

6.3. Both models **[1]** are also able to capture the increase in the systolic left ventricular pressure due to the rise in afterload induced by aortic stenosis **[2]**.

6.3.1. LAB MEDIA: Figure 5
6.3.2. LAB MEDIA: Figure 5 *Video Editor: please emphasize solid green data line in both graphs*

6.4. Upon remodeling and left ventricular compliance loss, the end-diastolic pressure-volume relationship becomes elevated, resulting in higher end-diastolic pressures and lower end-diastolic volumes **[1]**.

6.4.1. LAB MEDIA: Figure 5 *Video Editor: please emphasize red data line in both graph*

6.5. These phenomena, which are due to the inability of the left ventricle to relax and fill adequately, are successfully captured by the heart failure with preserved ejection fraction pressure volume loops in both the low- and high-dimensional models **[1]**.

6.5.1. LAB MEDIA: Figure 5 *Video Editor: please emphasize solid red data lines in both graphs*

6.6. The flow through the mitral valve data **[1]** highlights both the early relaxation **[2]** and atrial contraction phases **[3]**.

6.6.1. LAB MEDIA: Figure S2

6.6.2. LAB MEDIA: Figure S2 *Video Editor: please add E for early relaxation over peak Figure S2B*
6.6.3. LAB MEDIA: Figure S2 *Video Editor: please add A for atrial contraction over peak in Figure S2B*

6.7. Compared to the normal and stenosis profiles **[1]**, the heart failure with preserved ejection fraction flow was characterized by a slightly higher peak early relaxation-phase mitral flow **[2]** and a significantly diminished peak atrial contraction-phase flow **[3]**.

6.7.1. LAB MEDIA: Figure S2 *Video Editor: please emphasize green and grey data lines in Figure S2*
6.7.2. LAB MEDIA: Figure S2 *Video Editor: please emphasize red E peak in Figure S2*
6.7.3. LAB MEDIA: Figure S2 *Video Editor: please emphasize red A peak in Figure S2*

6.8. As illustrated in these myocardium stress maps **[1]**, elevated stresses can be observed in the heart failure with preserved ejection fraction due to the characteristic loss of ventricular compliance **[2]**.

6.8.1. LAB MEDIA: Figure 6
6.8.2. LAB MEDIA: Figure 6 *Video Editor: please emphasize red outlines in Systole HFpEF image*

Conclusion

7. Conclusion Interview Statements

7.1. **Caglar Ozturk**: To model the chronic effects of pressure overload and thus recapitulate the hemodynamics of HFpEF, it is critical to change the ventricular compliance in each simulation accordingly **[1]**.

7.1.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera (5.1., 5.3.)

7.2. **Luca Rosalia**: Diastolic stiffness can be parametrically investigated to simulate various phenotypes of diastolic dysfunction. This will enable us to more comprehensively characterize the effects of diminished compliance on disease **[1]**.

7.2.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

7.3. **Caglar Ozturk**: We hope that our work paves the way toward the creation of models that can advance our current understanding of HFpEF and supports the development of therapies for this condition **[1]**.

7.3.1. INTERVIEW: Named talent says the statement above in an interview-style shot, looking slightly off-camera

